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09/871,809	06/04/2001	Batsheva Kerem	24020X	3895

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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	9

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/871,809	KEREM, BATSHEVA	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 1-8 are pending.

Applicants' amendment filed February 4, 2003 (Paper No. 8) is acknowledged. Applicants' response, and Declarations of Dr. Hermona Soreq and Batsheva Kerem have been fully considered. Claims 1 and 5 have been amended, and claims 1-8 are examined.

Objection Withdrawn

2. The previous objection to the specification is withdrawn in view of applicants' amendment to the specification, and applicants' response at page 2 in Paper No. 8.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

3. The previous rejection of claims 1, 2 and 5-9 under 35 U.S.C.112, second paragraph, regarding the term "a disease", "an abnormal expression of genes" or "SR protein", is withdrawn in view of applicants' amendment to the claim, and applicants' response at pages 8-9 in Paper No. 8.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cell lines established from samples of cystic fibrosis patient resulting from an abnormal expression of genes caused by aberrant splicing in

cells, comprising administering to the cells, an naturally occurring alternative splicing factor (ASF) by transfected the cells with expression vector to produce the ASF, whereby the abnormal expression shifts towards normal expression of the gene, does not reasonably provide enablement for a method of treating individual suffering from a disease resulting from an abnormal expression of genes caused by aberrant splicing in cells, wherein the disease and the abnormal genes are not defined, comprising administering to the cells or to tissue or organs of the individual comprising the cells, an ASF, whereby the abnormal expression shifts towards normal expression of the gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-8 are directed to a method for treating individual suffering from a disease such as cystic fibrosis resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells or to tissue or organs of the individual comprising the cells, an ASF, whereby the abnormal expression shifts towards normal expression of the gene. The specification, however, only discloses [illegible] findings, which states that the method of invention concerns administering to the cells or to tissue or organs of the individual comprising the cells, an alternative splicing factor (ASF), e.g., any factor which is known to modulate alternative splicing, for example, members of the SR protein family including SF2/ASF, the heterogeneous ribonucleoprotein A1 (hnRNP A1), or the agonist of the naturally occurring ASFs, and the administration of the ASFs to the cells causes a shift in the expression of the gene responsible for genetic disease towards normal expression. There are no indicia that the present application enables the full scope in view of a method for

treating a disease resulting from an abnormal expression of genes as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the disease treated, the agonists of naturally occurring ASF administered, and the treating conditions of using ASF in various forms, e.g., as a protein product or an expression vector, which are not adequately described or demonstrated in the specification.

(2). The absence of working examples:

There are no working examples indicating the claimed methods in association with the variants except for the examples of several cellular and viral splicing factors that modulate the splicing pattern in epithelial cell line established from the sample of CF patient (Example 5, pages 14-17).

(3). The state of the prior art and relative skill of those in the art:

The prior arts, e.g., Mayeda *et al.* (Mol. Cell. Biology 13, 2993-3001 (1993)) teach the essential splicing factor SF2/ASF and hnRNP A1 modulate alternative splicing *in vitro* of pre-mRNAs. An excess of SF2/ASF prevents inappropriate exon skipping in natural β-tropomyosin

pre-mRNA, while an excess of hnRNP A1 does not cause inappropriate exon skipping in natural pre-mRNA; Nordqvist *et al.* (Mol. Cell. Biology 14, 437-445 (1994)) teach the adenovirus early region 4 proteins E4 open reading frame (E4-ORF3) and E4-ORF6 regulate major late mRNA accumulation by stimulating constitutive splicing. E4-ORF3 facilitates exon inclusion while E4-ORF6 facilitates exon skipping. However, the prior art does not teach the treatment of various diseases resulting from abnormal expression of genes caused by aberrant splicing in cells, and the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on identities of the disease being treated, the agonists of ASF administered, and the treating conditions for administering ASF as a protein product or an expression vector, to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method for treating a disease resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells an ASF, whereby the abnormal expression shifts towards normal expression of the gene. As indicated in the prior art (Mayeda *et al.*, Mol. Cell. Biology 13, 2993-3001 (1993)), hnRNP A1 can promote alternative exon skipping, however this effect is not universal and is dependent on the size of the internal alternative exon and on the strength of the polypyrimidine tract in the preceding of intron. The specification (e.g., Example 3, Table 2) also indicates transfection of p5T generated two splicing products: 24% of transcripts were aberrantly spliced (330 bp) and the rest (76%) were correctly spliced (513 bp), and transfection of p9T only generated 3% of transcripts being aberrantly spliced; however, transient cotransfection of p5T and pCG-A1 into COS-1 resulted in a substantial increase in aberrantly spliced transcripts (44%) and transient

cotransfection of p9T and pCG-A1 does not affect the p9T minigene pattern. Therefore, the invention is highly unpredictable regarding the outcome of the treatment without identifying the abnormal genes in the diseases or the agonists of ASF administered.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method for treating a disease resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells an ASF, whereby the abnormal expression shifts towards normal expression of the gene. The specification indicates the effect of overexpression of the cellular hnRNP A1 on the splicing of 3849+10 kb C->T or polyT minigenes, or the effect of overexpression of the viral E4-ORF6 on the splicing of 3849+10 kb C->T minigenes (Examples 2-5; Figs.3-7), where the mutation (3849+10 kb C to T) in the cystic fibrosis transmembrane conductance regulator (CFTR) gene has been linked to CF patients with abnormal epithelial function. However, the specification has not demonstrated the in vivo treatment of a disease, nor has indicated how to extrapolate the in vitro or ex vivo data to in vivo treatment, and there are no working examples indicating the effect of a known ASF in the treatment of the disease. Furthermore, the specification has not indicated the use of any agonist of a naturally occurring ASF, nor has demonstrated the administration of the protein product, ASF to cells is effective in shifting abnormal expression of the gene to normal expression and in the treatment of the disease. Moreover, there are no working examples indicating treating conditions such as effective amount of the ASF protein product for a specific disease in vivo. Since the specification fails to provide sufficient guidance on treating various diseases using a specific AFP or an agonist of the ASF, it is necessary to carry out further

experimentation to assess the effects of the ASF in treating the disease due to an abnormal expression of genes caused by aberrant splicing in cells.

(6). Nature of the Invention

The scope of the claims encompass treating a disease resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells an ASF, whereby the abnormal expression shifts towards normal expression of the gene, but the specification has not demonstrated the disease being treated with an AFP protein or an agonist of AFP protein in vivo, and the treating conditions for various diseases using the ASF protein product. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed method, the art is unpredictable regarding the outcome of the treatment, and the guidance and the teaching in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of ASF towards various diseases.

In response, applicants indicate based the information provided in the specification, the [illegible] and the Declaration of Dr. Hermona Soreq, a person skilled in the art would be able to carry out the claimed invention. In particular, the specification provides information on 2 different diseases (e.g., cystic fibrosis (CF) and spinal muscular atrophy (SMA); page 16, lines 22-29), 3 different types of cells (e.g., COS-1, HeLa and epithelial cell line established from a sample of CF patient; page 10, lines 1-13 and page 15, lines 15-22) and 7 different ASFs (e.g., ASF/SF2 hnRNPA1 etc., Figs 6 and 7; pages 3-4 of the response). Applicants further assert that two references (Nissim-Rafinia et al., Trends in Genetics 18, 123-127 (2002); Nakai et al., Gene

141 (2), 171-177 (1994) indicate various human diseases involve abnormal expression of genes caused by aberrant splicing in cells (page 4 of the response); and the Declaration of Dr. Hermona Soreq indicates the diseases caused by aberrant splicing is a known definition of disease, and ASFs are well-defined concept, thus a person skilled in the art would know, based on the instant specification, how to identify diseases caused by aberrant splicing and appropriate ASFs as well as how to use them in the treatment of disease (page 5 of the response). Applicants' response and the Declaration of Dr. Hermona Soreq have been fully considered, however, the argument is not found persuasive because the specification only indicates the in vitro or ex vivo treatment of cells having abnormal expression of genes caused by aberrant splicing in cells, and administration of an ASF to the cells an ASF shifts the abnormal expression towards normal expression of the gene, however, this shift is not universal (see the section of Predictability or unpredictability of the art; Fig. 4 and Table 2), thus, the outcome of the treatment is unpredictable. Furthermore, the specification does not indicate the in vivo or ex vivo treatment of the disease, and there is no teachings on how to extrapolate the in vitro data to in vivo treatment as indicated in the section above; the two references only provide the information on identification of various human diseases involving abnormal expression of genes caused by aberrant splicing in cells, they do not provide guidance on how to treat various diseases using ASF in vivo.

In the Declaration of Dr. Hermona Soreq, Paragraphs one and two state the education and career background of Dr. Hermona Soreq; Paragraphs 3-4 state Dr. Soreq has reviewed the instant application; Paragraphs 5-10 indicate the diseases caused by aberrant splicing is a known definition of disease, and ASFs are well-defined concept, thus a person skilled in the art would

know, based on the instant specification and the prior art (Annexes B and C), how to identify diseases caused by aberrant splicing and appropriate ASFs as well as how to use them in the treatment of disease. Declaration of Hermona Soreq has been fully considered, however, it is found not fully persuasive because the identification of the diseases due to aberrant splicing and the identification of ASF have been shown in the specification and the prior art, however, the treating conditions such as dose for in vivo treatment of the diseases have not been shown and the effects of ASFs in treating various diseases in vivo has not demonstrated, therefore, it requires additional guidance on the treating conditions to carry out further experimentation to assess the effects of ASFs as indicated in the section above.

7. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-8 are directed to a method for treating individual suffering from a disease (e.g., cystic fibrosis) resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells or to tissue or organs of the individual comprising the cells, an alternative splicing factor (ASF), whereby the abnormal expression shifts towards normal expression of the gene. The specification indicates that ASF may be administered to the cells by inserting a nucleotide sequence expressing the ASF in an expression vector, and the cells of the individual are transfected with the expression vector to produce ASF, or by attaching the expression vector to targeting moiety, e.g., antibody or a ligand of a specific receptor which can specifically bind to the membranes of the desired cells, and the expression vector being

administered systemically, or by administering ASF as the protein product itself (page 5, line 26-page 6, line 25). However, the specification only indicates the in vitro or ex vivo effect of administering AFP to the cell lines, e.g., the effect of overexpression of the cellular hnRNP A1 on the splicing of 3849+10 kb C->T or polyT minigenes, or the effect of overexpression of the viral E4-ORF6 on the splicing of 3849+10 kb C->T minigenes (Examples 2-5; Figs.3-7), it has not demonstrated the in vivo treatment of various diseases resulting from an abnormal expression of genes caused by aberrant splicing in cells, e.g., the administration of a ASF protein to cells is effective in shifting abnormal expression of the gene to normal expression and in treating the disease. Furthermore, there are no in vivo working examples indicating the treating conditions such as effective amount of the ASF for a specific disease, and the effect of the ASF in aberrant splicing of the genes and in the treatment of disease. Without guidance on the treating conditions of ASF on the disease, one skilled in the art would not know how to use the ASF. The lack of description in the treatment of the disease using the ASF as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

In response, applicants indicate the specification demonstrates the effect of overexpression of DNA sequences encoding ASF proteins on aberrant splicing, which results in the production of the ASF protein in the cell, and the specification provides sufficient number of Examples (Examples 1-5) to indicate possession of the invention; and the Declaration of Dr. Batsheva Kerem demonstrates that a person skilled in the art would understand the full scope of the invention and know how to use ASFs for the treatment of diseases by restoring gene function

(pages 6-7 of the response). Applicants' response and the Declaration of Dr. Batsheva Kerem have been fully considered, however, the argument is not found persuasive because the specification only indicates the in vitro treatment of cells having abnormal expression of genes caused by aberrant splicing in cells, and CFTR ex vivo treatment of cell line derived from a polyp of a CF patient, although the function is restored toward normal values after transfection of the cells with ASF or an ASF agonist (Annex B), however, the specification does not describe the in vivo treatment of the disease using ASF protein or ASF agonist. Furthermore, there is no teaching on how to extrapolate the in vitro or ex vivo data to in vivo treatment, thus, the specification does not fully describe using the ASF in the treatment of the diseases caused by aberrant splicing.

In the Declaration of Dr. Batsheva Kerem, Paragraphs one and two state the education and career background of Dr. Batsheva Kerem; Paragraph 3 states Dr. Kerem is the inventor, and the invention is directed to a method of treating a disease resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising administering to the cells an ASF, whereby the abnormal expression shifts towards normal expression of the gene; Paragraphs 4-6 [illegible] the examples in the specification and the known methods enable a person skilled in the art to use ASFs including an ASF agonist for the treatment of diseases by restoring gene function, e.g., Example 5 and Annex B; Paragraphs 7-10 indicate the methods of cloning genes and expression them in cells are considered routine methods in the prior art, and using different ASFs than those described in the specification is also a matter of routine work, although the described examples are related to the treatment of cystic fibrosis, it would be able to extrapolate from the specific example to general concept for the treatment of other diseases. Declaration of

Batsheva Kerem has been fully considered, however, it is found not fully persuasive because the specification docs not describe the in vivo treatment of the disease using ASF protein or ASF agonist, and how to extrapolate the in vitro or ex vivo data to in vivo treatment, thus the specification does not fully describe using the ASF in the treatment of the diseases caused by aberrant splicing.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8 are indefinite because the claims lack essential steps in the method of treating an individual suffering from a disease resulting from an abnormal expression of genes caused by aberrant splicing. The omitted step is the outcome of the treatment, it is not clear what effect the administration of ASF would produce in the treatment of disease. Claims 2-8 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

In response, applicants indicate claim 1 has been amended to include the step of treating the disease (page 8 of the response). The argument is not found persuasive because the term "treating said disease" does not reflect the treatment is effective, thus it is not the endpoint of the method claim.

6. Claims 3 and 4 are indefinite because the claim recites a mutation of "3849+10kB C->T" or "5T allele", but the claim does not identify the gene having the mutation, therefore it is not clear which gene has the mutation.

Conclusion

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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May 11, 2003